



# **DIRECT TO CONSUMER GENETIC TESTING**

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# LEARNING OBJECTIVES

## List

- List common types of genetic information provided by Direct To Consumer Genetic Testing (DTC- GT) companies.

## Describe

- Describe history of DTC-GT and attempts to regulate industry

## Summarize

- Summarize why DTC-GT results can be misleading or inaccurate

## Clarify

- Clarify necessity to repeat DTC-GT results in CLIA lab

## Discuss

- Discuss ethical issues related to DTC-GT

# DIRECT TO CONSUMER GENETIC TESTING (DTC-GT)

Providing genetic testing via internet without involvement of clinicians;  
typically use saliva kits

Growing rapidly due to large decrease in sequencing costs and  
increasing public data on human genetic variation

- Human Genome project: 1990-2003 provided researchers with reference genome
- Common variant types: SNP (600 million), insertions and deletions
- dbSNP- public archive of variants (both clinically relevant and neutral)
- ClinVar- public archive of variants (suspected clinically relevant)
- GWAS- (genome wide associated studies) examining markers across complete sets of genomes to identify genes associated with disease risk

# COMMON TYPES OF DTC-GT

Nutrigenetics- (weight control, food intolerance and sensitivity)

Fitness and talent- (performance and injury)

Recreational infotainment- (eye color, hair thickness, ear lobe type)

Health-related

- GWAS (diabetes, heart disease, gall bladder, atrial fibrillation)
- Mendelian conditions: breast cancer, Parkinson, hemochromatosis as well as carrier tests (cystic fibrosis, Tay-Sachs, Sickle cell)

Ancestry- (ethnic background; often connects users to others sharing common DNA markers).

# DTC-GT



Despite claims that DTC companies lack scientific evidence, accuracy, or ethical practices.....



More than 26 million consumers have been tested by 4 companies



Market at one billion USD in 2020 and predicted to grow to 6 billion by 2028

# DTC-GT ISN'T JUST FOR HUMANS

For felines suspected of an inherited disease; helps veterinarian refine treatment

For dogs- from testing 6000 Siberian Huskies to identify 98.6kb duplication associated with blue eyes and heterochromia to vets testing for atopic dogs

# DTC-GT BEGAN IN 2006, SO DID ITS PROBLEMS....

Tests not performed in CLIA certified labs

Tests not clinically validated

Tests may lack clinical utility

No pre-test and post-test counseling, or someone to provide guidance in post-test decision-making

State regulators and US FDA introduced regulations on DTC practice in 2008

Allows consumers increased anonymity and privacy by bypassing medical record

# US GOV ACCOUNTABILITY OFFICE STUDY

Sent samples to 4 DTC companies and received different results

One donor was given reports that he was a below average, average and above average risk for prostate cancer and hypertension

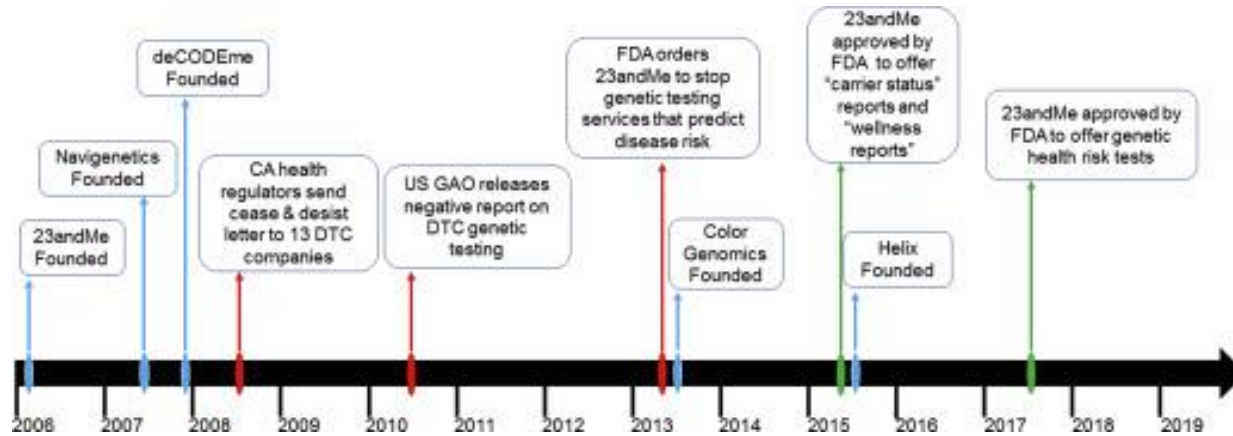
Two companies claimed to predict athletic performance and sport best suited to future skill set

2 companies offered personalized supplements indicated they could cure disease; one company actually said their supplement could repair DNA damage (there is no scientific basis for the claim)

**FDA issued “cease and desist” order to 23andMe to immediately discontinue personal genome services in Nov 2013.**



# ATTEMPTS TO REGULATE DTC COMPANIES



# NUTRIGENETICS

Suggest dietary changes to prevent pathogenesis of specific diseases based on one's genetic background

Defined based on limited set of genetic markers

# NUTRIGENETICS

Reliable for monogenic diseases: ie. galactosemia, PKU

Not reliable for multifactorial traits ie. obesity, vitamin levels, type 2 diabetes, cardiovascular disease

45 companies offering nutrigenetics ( most in North Am 19, Europe 21 )

Fee: 39% >\$200; 36% (\$100-\$200); 25% <\$100

Food intolerance/ sensitivities: Lactose 40%; Caffeine 33%; Alcohol 18% ; Salt 11%, Fructose 4 %

Metabolism: Lipid 29%; Carbohydrate 13%; Vit D 29%, Vit C 22%, (Vit A, B6 and B12-20%); Iron 9%

# NUTRIGENETICS DTC COMPANIES

9% provided variant investigated (dbSNP ID); 22% only gene name; 65% do not list gene or variant investigated

Of 9% providing dbSNP ID for 64 variants, only 50% had GWAS assoc with trait of nutritional interest; thus, 50% provided false evidence of assoc.

>80% offered personalized results with recommendations

11/45 companies had disclaimers

# CLAIMS BY DTC-GT FOR SPORTS PERFORMANCE/TALENT

Discover how your genes contribute to your athletic traits

Personalize your training based on your sports genetic results

Take advantage of your strengths and overcome your limitations

We provide parents and coaches info on child's predisposition of success in team or individual speed/power or endurance sports

Valuable in outlining training and conditioning programs necessary for athletic and sport development

Use DNA results to help you lose fat, get lean/fitter, and build muscle

# SCIENTIFIC EVIDENCE FOR GENETIC TESTING FOR SPORTS TALENT

Webbtor reported on 39 companies provided DTC for sports, exercise performance, or injury in 2015

## Median of 6 variants tested

- ACE II genotype- endurance
- ACTN3 RR genotype- speed and power;
  - 31% UK has this genotype; predicts 2-3% of interindividual variability in sprinting performance

## International Federation of Sports Medicine Scientific Commission:

- Predictive value of such tests in context of training responses and talent ID in sport is virtually zero
- No evidence that genetic tests provide info for predisposition to particular sport, training program, or exercise-related injury

# DTC-GT IN SPORTS

GT should only be performed with proper informed consent; impossible when consumer has not received relevant info about GT to understand risks, benefits, limitations and implications

GT in children problematic as child does not have capacity for consent; only test if management of child's health would be significantly altered.

ASHG pos statement; DTC testing discouraged in children until companies can assure quality, accuracy, validity of testing and pre and post-test counseling.

Ethical issues: psychosocial consequence: impaired self esteem, social stigma, failure to engage in activities that could have provided lifetime satisfaction

# WHAT ARE THE PITFALLS OF DTC-GT FOR CLINICALLY RELEVANT GENES?

Not every gene or genetic variant associated with specific diseases are tested

No genetic specialist to help interpret result or help guide medical decision-making

Misunderstanding of results may lead to needless medical interventions or false reassurance



# DTC-GT FOR MULTIFACTORIAL CONDITIONS

US FDA limits the type of health-related claims DTC companies can market.

In 2017, 23 and Me authorized to test 10 multifactorial conditions: Parkinson, late onset Alzheimer's, celiac, A-1-A, early onset primary dystonia, factor XI deficiency, G6PD deficiency, Gaucher type 1, hemochromatosis, thrombophilia.

Results based on limited list of genetic variants

Variants tested are not necessarily causal of these multifactorial conditions  
ie. (HLA testing for Celiac, APO E for Alzheimers)

# DTC-GT FOR MENDELIAN DISEASES

Causative genes only tested for targeted number of path variants; genes are NOT sequenced

- Ex. Parkinson is caused by variants in LRRK2, GBA, SNCA1 and PARK2/PARKIN
- But only one variant in LRRK2 and one variant in GBA tested.

Customers can request raw genotyping data including variants Mendelian diseases such as those recommended by ACMGG.

Consumers may pay a third party company to analyze additional variants using public databases; majority of classifications in some publicly available databases are incorrect

# DTC- GT FOR BREAST CANCER

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23 and Me received FDA permission to test 3 BRCA1 and BRCA2 gene variants in 2018

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Pathogenic BRCA1 & BRCA2 variants increase risk for breast cancer by 50-70% and ovarian cancer by 10-50% by age 70

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BRCA genes repair DNA double strand breaks

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Path variants in BRCA genes decreases repair capacity leading to accumulation of DNA mutations leading to cancer.

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>1500 different BRCA1 variants and >1700 BRCA2 variants are linked to increased risk for breast and ovarian cancer

# 23 AND ME TESTING BRCA1/2 FOR 3 VARIANTS

Genetic counseling prior to such testing is recommended by the US National Comprehensive Cancer Network

Although 23 and Me is only testing 3 BRCA variants, its promotional material implies capacity to detect all path variants

These 3 variants found in 2% of AJ individuals and <0.1% of gen pop

Thus, 23 and Me's BRCA testing is unhelpful for general pop and misleading when negative

# ISSUES WITH POSITIVE BRCA RESULTS

Results difficult to interpret without aid of genetic specialist

Induce stress for individual and family members

High false positive rate for DTC-GT

60% of customers use third-party tools to aid interpretation

Disclaimer: BRCA1/2 and other Personal Genome Service test results are not meant to be diagnostic; nuance is lost on most consumers

# ISSUES WITH POSITIVE BRCA DTC-GT RESULTS

Needs to be confirmed  
in CLIA lab

Unlikely confirmatory  
DNA testing will be  
covered by insurance for  
individuals who don't  
meet clinical guidelines

Individuals with  
confirmed positive results  
should discuss long-term  
cancer risk-reducing  
strategies with physician

Only 30% of customers  
of DTC genetic testing  
share results with their  
physician

# CONSUMERS EXPLORING DTC-GT RESULTS USING THIRD PARTY INTERPRETATION WEBSITES

2 patients used 3<sup>rd</sup> parties to analyze raw data and requested medical interventions based on pathogenic variants present

Follow up clinical testing in CLIA lab revealed pathogenic variant results were false positives

DTC-GT can have false positive and false negative results

Clinicians need to order confirmatory testing in CLIA lab

Medical professionals may need to spend increasing amounts of time investigating genetic results of dubious validity

# CLINICAL CONFIRMATION CRUCIAL FOR DTC-GT

Ambry tested 49 samples to confirm DTC-GT results

Providers ordering confirmation were GC/geneticists (41%), oncologists (20%)

Testing cancer genes (88%), CF (8%), FMF (2%), connective tissue dis (2%)

40% of variants in a variety of genes reported in DTC-GT raw data were false positives

Errors identified in 8/25 BRCA1/BRCA2 variants, 3/5 CHEK2 variants, 3 TP53 variants, 1 ATM variant, 2 MLH1 variants, 1 of 2 connective tissue variants.

Additionally, 8 variants (5 on one patient's report) were misclassified by third party interpretation services as "increased risk" but were actually benign



# NEED CONFIRMATION TESTING OF VARIANTS IN CLIA CERTIFIED LAB

Given shortage of genetic counselors or other highly trained genetic professionals, concern how DTC results may be interpreted and used among other HCPs

49 cases represent:

- Patients who shared DTC-GT results with HCP
- HCPs who understood need for confirmatory testing

Increased financial burden DTC tests place on our health care system

# ETHICAL ISSUES IN DTC-GT

Questionable  
analytic and  
clinical validity of  
tests

Inadequate  
informed consent

Misleading  
advertising

Testing in children

Research uses  
and  
commercialization  
of genomic data

# DTC GENETIC TESTING ON MINORS

Am Acad Ped guidelines: Predictive genetic testing for adult-onset conditions should be deferred until child can consent

AMA opinion: Genetic testing in children should only be performed under care of physician with appropriate counseling when there are effective preventative and treatment measures

DTC allows parents to order any publicly available test on their child; child is unlikely to understand result and later in life may not wish to have had the testing performed

# DTC-GT ON CHILD LED TO ERRONEOUS MEDICAL PROCEDURE

15 year old girl underwent DTC-GT

Identified a pathogenic PKP2 gene variant assoc with arrhythmogenic right ventricular cardiomyopathy

An erroneous cardiac MRI test, led to placement of implanted cardioverter defibrillator

Confirmatory testing in CLIA lab showed no PKP2 gene variant; repeat cardiac MRI was normal

Device was removed

# PATIENT PRIVACY

Commercialization of DNA sequencing reveals personal information about disease susceptibility, traits and predispositions for patient and relatives

DTC genetic testing companies- not covered by HIPAA

23 and Me has 25 page “terms of service” and 29 page “privacy statement” explaining sample handling and use by third parties. Poorly understood by DTC participants

23 and Me reserves right to use and share customer data with partners (even after customers delete their account) as long as individual cannot be “reasonably identified”.

23 and Me has sold de-identified data to pharmaceutical companies

# WHEN TO REFER PATIENT TO GENETIC SPECIALIST



## **Patient presents DTC genetic results and...**

Not enough time to research genetic cause of disease, test methodology, and interpret significance of result

Too busy to explain the test result and need for confirmatory testing in a language patient can understand

Unsure how to order the most cost-effective confirmatory testing

Prefer a genetic specialist order/ interpret the confirmatory test and send patient back to you for medical management



## **To find a genetic counselor near you:**

NSGC.org and click "Find a Genetic Counselor"

# REFERENCES

Dinulos, Mary et al. The Impact of Direct-to-consumer Genetic Testing on Patient and Provider. Clin in Lab Med, 2020 Mar; 40(1):61-7.

Floris, Matteo et al. Nutrients 2020 Feb;12(2) 566; PMID: [32098227](#)

Horton, Rachel, et al. Emerg Top Life Sci 2019 Nov 27;3(6):669-74 PMID: 32915220

Moscarello, Tia et al. Direct-to-Consumer Raw Genetic Data and Third-Party interpretation Services: more Burden than Bargain? Genet Med 2019; 21; pp.539-41.

Niemiec, Emilia et al. Current ethical and legal issues in health-related direct-to-consumer genetic testing. Per Med.2018Mar;15;137

Petersen, Lauren et al. Lessons Learned from Direct-to-Consumer Genetic Testing; Clin Lab Med, 2020, Vol 40, 83-92.

Tandy-Connor, Stephany et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 2018;20(12): 1515-21. PMID: 29565420

Webborn, Nick et al. Direct to Consumer Genetic testing for predicting sport performance and talent identification: Consensus Statement: Br J Sports Med 2015 Dec;49 Dec;49 (23) 1486-91. PMID: [26582191](#)

US Food and Drug Administration: Warning letter. <https://wayback.archive-it.org/7993/20170111084101/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm>